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Case Report
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Breaking the Cycle of Recurrent *Clostridioides difficile* Infections: Can Probiotic Bacteria Contribute?

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Abstract

Recurrent *Clostridioides (C.) difficile* Infection (CDI) is a major complication of the management of CDI and affects between 12% to 24% of all CDI patients. We report a case of CDI triggered by therapy with the broad-spectrum antibiotic cefuroxime, followed by three episodes of recurrent CDI. The initial CDI and the first recurrence were treated with vancomycin combined with a three-strain probiotic. This treatment was initially successful but was soon followed by a new recurrence. The second recurrent CDI was treated with vancomycin combined with a mono-strain synbiotic (one probiotic strain plus fructooligosaccharides) which was also only transiently successful. The third recurrent CDI was treated with vancomycin combined this time with a nine-strain synbiotic resulting in a sustained elimination of *C. difficile*. The three different probiotic bacteria containing products were characterized regarding their ability to inhibit the *in-vitro* growth of *C. difficile*. All products inhibited the growth of *C. difficile*, with the nine-strain synbiotic being the most effective. The clinical observations and the results from the *in-vitro* experiments suggest that certain products containing probiotic bacteria might contribute to break the cycle of recurrent CDI. More research, including clinical studies, should be performed to investigate the potential role of probiotics/synbiotics in the management of recurrent CDI.

Keywords: Probiotics; Synbiotics; Recurrent *Clostridioides (Clostridium) difficile* infection; Antibiotic therapy

Introduction

Clostridioides difficile (formerly known as *Clostridium difficile*) infections have increased strongly during the last three decades, mainly driven by an increased usage of broad-spectrum antibiotics [1]. Originally mainly considered as a problem acquired by patients in hospitals or other healthcare institutions (e.g. nursing homes), today a significant proportion of CDI is community acquired [2]. After effective treatment of an initial CDI, recurrence occurs in 15% to 35% of patients [3]. Second and subsequent recurrences are even more common after the first recurrence [4]. The cause for CDI recurrence is assumed to be a disturbed gut Microbiota resulting in an impaired colonization resistance, which is normally provided by a diverse and balanced community of gut bacteria [5]. The reduced colonization resistance can allow a relapse of the original infection (resulting from endogenous persistence of the same *C. difficile* strain) or a reinfection (acquisition of a new strain from an exogenous source) [6]. Most recurrences occur within the first 30 days after completing a course of CDI therapy [7].

Our case report describes a patient suffering from a first CDI, caused (most likely) by treatment with the broad-spectrum antibiotic cefuroxime during a hospital stay. This initial CDI and following recurrent CDI episodes were treated with vancomycin and a follow-up treatment with metronidazole. Identical antibiotic therapy was employed for the treatment of all different CDI episodes, however, a variety of products containing probiotic bacteria were administered to support the colonization resistance of the gut Microbiota. While treatment of the CDI episodes was initially always successful, confirmed by absence of *C. difficile* toxins and glutamate dehydrogenase, these treatment successes were short lived. Only when the antibiotic therapy was combined with the coadministration of a nine-strain synbiotic, the cycle of CDI recurrences came to a stop. Assuming that the differences in treatment outcomes might be related to differences among the properties of the products containing probiotic bacteria, their effects on the *in-vitro* growth of *C. difficile* were characterized.

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Case Presentation

First hospitalization

On April 13th, 2017, a 62-year-old woman was hospitalized because of suspected ovarian cancer. The patient had a history of kidney cystic disease, hypertension, ischemic heart disease, circulatory failure, colon diverticulosis and chronic gastritis. Since 2015 the patient was on chronic dialysis therapy. During her hospital stay, which lasted until April 28th, she received (among other interventions) cefuroxime, 1,500 mg, TID, IV for 14 days.

Initial *C. difficile* infection (Figure 1): On May 02nd, 2017, four days after her discharge, the patient was re-admitted to hospital because of intestinal inflammation, abdominal pain and diarrhea. Testing for *C. difficile* toxin at admission was positive, leading to treatment of the diagnosed CDI with vancomycin 250 mg, OD, PO, accompanied by administration of two capsules of a three-strain probiotic product (Trilac) per day. After 10 days of treatment the patient tested negative for *C. difficile* toxin and Glutamate Dehydrogenase (GDH). The patient was discharged from hospital and recommended to take metronidazole, 500 mg, TID, PO, and the three-strain probiotic (Trilac), two capsules per day.

First recurrent CDI

On May 23rd, 2017, ten days after her last discharge from hospital, the patient was again admitted to hospital, this time because of a recurrent CDI. At admission the patient tested positive for *C. difficile* toxin and GDH. Treatment was again with vancomycin, 250 mg, OD, PO, and the three-strain probiotic Trilac (two capsules per day). After 8 days of treatment the patient tested negative for *C. difficile* toxin and GDH. The patient was discharged from hospital with the recommendation to take metronidazole, 500 mg, TID, PO, and the three-strain probiotic (Trilac), two capsules per day.

Second recurrent CDI

On June 22nd, 2017, three weeks after her last discharge, the patient was admitted to hospital because of recurrent CDI, confirmed by positive test for the presence of *C. difficile* toxin and GDH. Treatment was again with vancomycin, 250 mg, OD, PO, but this time accompanied by a mono-strain synbiotic (one probiotic bacterial strain plus Fructooligosaccharides (FOS) as prebiotic component) preparation (Acidolac). Two sachets of the synbiotic were administered per day. After nine days of treatment the patient tested negative for *C. difficile* toxin and GDH. She was discharged from hospital with the recommendation to take metronidazole, 500 mg, TID, PO, and the mono-strain synbiotic (Acidolac), two sachets per day.

Third recurrent CDI

On July 31st, 2017, four weeks after her last discharge, the patient was again admitted to the hospital because of recurrent CDI, confirmed by positive tests for *C. difficile* toxin and GDH. Treatment was with vancomycin, 250 mg, OD, PO this time accompanied by the administration of a nine-strain synbiotic (Vivatlac). Two capsules of the nine-strain synbiotic were administered per day. After 12 days of treatment the patient was tested negative for *C. difficile* toxins and GDH and was discharged in good condition for further treatment on an outpatient basis. After her discharge the patient was treated with metronidazole, 500 mg, TID, PO for seven days and two capsules of the nine-strain synbiotic per day for a month. Since the last discharge of the patient from the hospital on August 12th, 2017 CDI has never recurred.

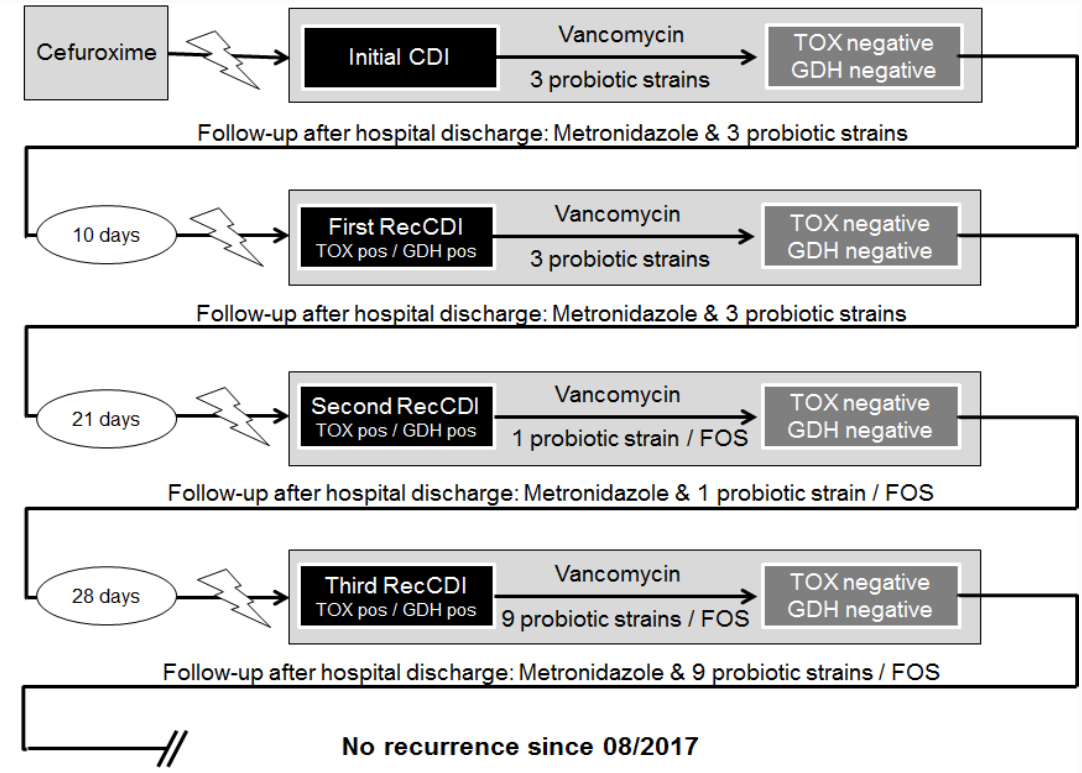

Figure 1: Overview of the sequence of clinical case events. Events in grey boxes occurred in the hospital. Rec CDI-recurrent C. *difficile* infection, TOX pos– C. *difficile* toxin positive.
GDH pos: Glutamate Dehydrogenase Positive; FOS: Fructooligosaccharides

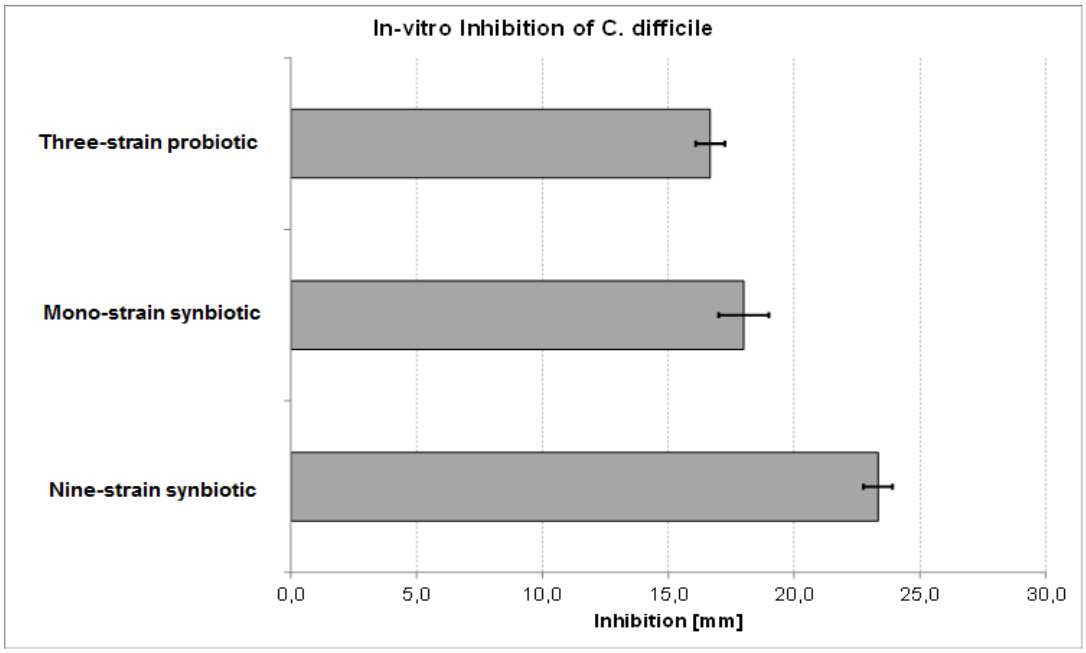

Figure 2: *In vitro* inhibition of the growth of *C. difficile* by the three products containing probiotic bacteria administered to the patient of the case report. Bars indicate the average from three independent experiments and the error bars the respective standard deviations.

Inhibition of the *in-vitro* growth of *C. difficile*: *In vitro* growth inhibition experiments were performed as described previously [8] by using a ribotype 001 *C. difficile* (ATCC® 9689™) reference strain purchased from ATCC, Manassas, Virginia, USA [9]. All products containing probiotic bacteria employed during the treatment of the patient are commercially available and were purchased for the in vitro experiments. The three-strain probiotic Trilac (Kortex Pharm, Warsaw, Poland) contains a total of 1.6×10^9 Colony Forming Units (CFU) per capsule, and is a mixture of *Lactobacillus acidophilus* (43.75%), *Lactobacillus delbruecki subsp. bulgaricus* (12.5%) and *Bifidobacterium lactis* (43.75%). The mono-strain synbiotic Acidolac (Polpharma S.A., Gdansk, Poland) contains 4×10^9 CFU *Lacticaseibacillus rhamnosus* GG ATCC 53103 and 800 mg FOS per sachet. The nine-strain synbiotic Vivatlac (Vivatrex, Rees, Germany) contains 63 mg of the prebiotic FOS and a total of 4.5×10^9 CFU of bacterial probiotic bacteria per capsule as a mixture of *Lactococcus lactis* Ll-23 (20%), *Lactobacillus helveticus* SP 27 (20%), *Bifidobacterium longum* Bl-05 (15%), *Bifidobacterium breve* Bb-03 (10%), *Lacticaseibacillus rhamnosus* Lr-32 (10%), *Streptococcus thermophilus* St-21 (10%), *Lacticaseibacillus casei* Lc-11 (5%), *Lactiplantibacillus plantarum* Lp-115 (5%), and *Bifidobacterium bifidum* Bb-02 (5%). Results of the *in-vitro* growth inhibition of *C. difficile* by samples containing 10^6 CFU of the respective product are shown in Figure 2.

Discussion

The present case represents a clinical sequence of events that physicians encounter with up to a third of their CDI patients: Initial CDI caused by therapy with a broad-spectrum antibiotic followed by several episodes of recurrent CDI [3,4]. A disturbed gut Microbiota resulting in a reduced colonization resistance is hypothesized to be the cause, or at least to contribute to this clinical picture [5]. Consequently, supporting the colonization resistance of the gut Microbiota by administration of probiotic bacteria can be suggested as a therapeutic option for the management of recurrent CDI. Currently, the best evidence supporting this hypothesis exists for Fecal Microbiota Transplantation (FMT), which has demonstrated positive effects in patients with multiple recurrence of CDI and failed appropriate antibiotic treatments [10]. However, as FMT involves the transfer of an ill-defined mixture of bacteria, it is associated with some risks [11]. Among these risks are (i) the transfer of potentially infectious pathogens from the donor to the recipient and (ii) the development of auto immunological disorders. Therefore, supporting the colonization resistance of the gut Microbiota by administration of products containing well defined and characterized probiotic bacteria can be assumed to be a safer option. However, selecting a probiotic or synbiotic product from the huge number of different products available remains a challenge. While not providing evidence-based insights, the case study hints that products containing probiotic bacteria could have the potential to break the cycle of recurrent CDI, but also indicates that specific product features might be needed to achieve this objective. Observations of the patient case and the results from the *in-vitro* experiments suggest that more complex mixtures of probiotic bacteria, containing a larger number of different probiotic bacterial strains, supported by the presence of a prebiotic component (e.g., FOS), might be a better choice compared to mono-strain or low number multi-strain products. That multi-strain probiotics or synbiotics have better inhibitory effects on the growth of pathogenic bacteria has been shown in other studies [12] and theoretically rationalized [13]. We hope that the findings described in the presented case report will trigger a broader interest in the potential role that probiotics and synbiotics might play in the management of recurrent CDI, as only controlled clinical trials will reveal the evidence needed to judge their role in the management of recurrent CDI.

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